Management of allergy transfer upon solid organ transplantation

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Management of allergy transfer upon solid organ transplantation

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Key words: solid organ transplantation, allergy transfer, immunosuppression, management, anaphylaxis, Immunoglobulin E, IgE

Abbreviations: Solid Organ Transplantation (SOT), Swiss Transplant Cohort Study (STCS), Skin Prick test (SPT), IgE-producing B-cells (IgE-Bcs)

Abstract

Allergy transfer upon solid organ transplantation has been reported in the literature although only few data are available as to the frequency, significance and management of these cases.

Based on a review of 577 consecutive deceased donors from the Swisstransplant Donor-Registry, three cases (0.5%) of fatal anaphylaxis were identified, two because of peanut and one of wasp allergy. The sera of all three donors and their ten paired recipients, prospectively collected before and after transplantation from the Swiss-Transplant-Cohort-Study, were retrospectively processed using a commercial protein microarray fluorescent test. As early as five days post-transplantation, newly acquired peanut-specific IgE were transiently detected from one donor to three recipients, of whom one liver and lung recipients developed grade III anaphylaxis. Yet, to define how allergy testing should be performed in transplant recipients and to better understand the impact of immunosuppressive therapy on IgE sensitization, we prospectively studied five atopic living-donor kidney recipients. All pollen-specific IgE and >90% of skin prick tests remained positive 7 days and 3 months after transplantation indicating that early diagnosis of donor-derived IgE sensitization is possible. Importantly, we propose recommendations with respect to safety for recipients undergoing solid-organ transplantation from donors with a history of fatal anaphylaxis.

1. Introduction

Anaphylaxis is a frequent cause of hospitalization with an estimated annual fatality rate of approximately 0.5 per 1'000'000. Food allergy being the most common cause for anaphylaxis in children and young adults, death due to food allergy was found in about 25% of the reported patients (1). Peanuts or tree-nuts were the causative allergens in more than 70% of the cases in which the responsible allergen was identified. Other allergens frequently involved in fatal anaphylaxis are fish, milk and egg but also bee and wasp venom, and drugs (1).

The first cases of transplant associated-allergy transfer were reported after hematopoietic stem cell transplantation, likely caused by IgE-specific B cells or T helper type 2 cells that were co-transferred with hematopoietic stem and progenitor cells (2). Subsequently, cases of allergy transfer were also described after solid organ transplantation (SOT), predominantly after liver, lung or combined pancreas-kidney transplantation (Table 1) (3–11). Only very few data are available as to the frequency, significance and mechanisms of IgE transfer in the setting of SOT.

In addition, the impact of immunosuppression on IgE sensitization is poorly understood. The objectives of this study were: (1) to identify the frequency and significance of allergy transfer based on retrospective analysis from the Swiss-transplant-Donor Registry and the Swiss-Transplant-Cohort-Study (STCS); (2) to evaluate if allergy testing is feasible early after solid organ transplantation; (3) to make recommendations for the diagnosis and management of allergy transplant after SOT.

2. Material and methods.

2.1 Donor-to-recipient IgE transfer

We retrospectively reviewed the data of 577 consecutive deceased donors from the Swisstransplant Donor-Registry (from January 2012 to May 2017) and identified three donors who died of anaphylaxis. In this registry, the individual history of severe allergy was not recorded. We then collected the prospectively stored sera of each donor-paired recipient from the STCS (Table 2) (12), a prospective multicenter cohort including all SOT performed in Switzerland as of May 2008. Sera of the recipients are prospectively collected at baseline (day of transplantation), 6 and 12 months after transplantation. In addition, sera were individually collected throughout the different centers at specific time points after transplantation. To assess the IgE profile of the donor and recipient's sera, a commercial protein microarray fluorescent test bearing recombinant allergen molecules (ISAC™, ThermoFisher Scientific) was used. ISAC standardized units (ISU-E) were assessed using a cut-off value defined at 0.35 ISU. All recipients gave written informed consent for participation. Local ethics IRB committee (ID 2017-1058, CCER-GE) and Swisstransplant approved the study.

2.2 Immunosuppression and IgE sensitization

Skin prick tests (SPT), specific IgE values and clinical symptoms were monitored in five adult living-donor kidney transplant recipients suffering from symptomatic allergic rhino-conjunctivitis between November 2016 and August 2018. The rhino-conjunctivitis score was based on the subject's nasal (runny nose, blocked nose, sneezing, itchy nose) and eye symptoms (gritty feeling/red/itchy eye and watery eye) using a 3-point scale (none=0, slight symptoms=1, moderate symptoms=2, and severe symptoms=3) for the six symptom classes. All recipients gave written informed consent (ID 2018-00965, CER-VD).

3. Results

3.1 Donor case 1

One young organ donor died of peanut-allergy-induced anaphylaxis leading to cardiac arrest with subsequent brain death. Upon admission, tryptase was > 100ng/ml (normal results: <10ng/ml). With the consent of the relatives, the heart, lungs, liver and kidneys were procured for transplantation. The liver was further split and transplanted into two recipients (Figure 1A). On post-transplant follow-up, the kidney of one recipient had to be explanted within the first week post-transplant because of multiple surgical complications and the patient was subsequently excluded from the analysis. Recombinant peanut-specific IgE known to be major elicitors of clinically relevant allergy (13) could be detected in the donor (Ara h1: 42 ISU-E, Ara h2: 85 ISU-E, Ara h3: 36 ISU-E, and Ara h6: 61 ISU-E), and in both liver (LiverR1, LiverSplitR2) and lung recipients (LungR3), but neither in the kidney nor in the heart recipients of the same donor (Figure 1B-C).

In the case of LiverR1, an inadvertent oral ingestion of two peanuts on POD 11 resulted in stomach pain, vomiting and transient dyspnea. LungR3 underwent an oral challenge on POD 30 with a starting dose of 6mg peanut (=1.5 mg peanut protein ED05). After the fifth dose, the patient developed urticaria, acute asthma and stomach pain. The oral challenge was negative in LiverR2. However, the test was performed nine months after transplantation when peanut-specific IgE were not detectable anymore in the patient's sera.

LiverR1 and LungR3 responded to treatment with antihistamines, glucocorticoids and inhaled salbutamol. Two years after transplantation, an oral challenge with peanuts was well tolerated by recipient LiverR1 after SPT had become negative, whereas LungR3 refused a repeat oral challenge. Of note, recipients with de novo transferred-IgE were atopic as defined here by the presence of specific IgE against, pollen, animal dander or house dusts mites (Figure 1D). These data indicated that de-novo occurrence of specific IgE to recombinant peanut allergen IgE (Ara h1, 2, 3 and 6) may predict allergy transfer in SOT.

3.2 Donor cases 2

The second donor had a history of wasp allergy and developed cardiac arrest after a wasp sting despite of the self-application of epinephrine. Analysis of the sera upon admission showed a tryptase level of 3.95 ng/ml without significant elevation of specific IgEs to crude and

recombinant wasp venom allergens (rVes v5 1.1 ISU-E, wasp IgE negative). An ISAC performed in both the donor and two recipients (kidney and lung) did not show any IgE transfer. In this case, failure to document an elevation of the tryptase or specific IgEs does not exclude the diagnosis of IgE-mediated anaphylaxis in light of the personal history (14, 15) although a non-IgE mediated-anaphylaxis (mast cell liberation, IgG- or complemented-mediated) might be possible. Overall, these data suggest that if the exact nature of an allergy is not appropriately documented in the donor, the pre-test probability of identifying allergy transfer is likely reduced.

3.3 Donor cases 3

The third donor had an anaphylactic reaction with cardiac arrest supposedly mediated by peanut ingestion. On admission, tryptase was elevated (38.1 ng/ml) whereas serum IgE (measured by UniCAP™, ThermoFisher) to peanut (3,04 kUI/l), hazelnut (6,74 kUI/l), almond (1,14 kUI/l), cashew nut (1,27 kU/l) and pistachio (3,24 UI/l) were only moderately elevated. Interestingly, in the sera of the donor a high level of nAct d1 (actindin) was found, a serological marker which can be associated with severe allergic reactions to kiwi (16). However, the serological analysis of the three recipients of this donor, i.e pancreas-kidney, heart-kidney, and liver showed no peanut and kiwi IgE at six months' post-transplantation. Interestingly, the donor was also highly sensitized to animals (rCanf1:87 ISU-E, rCanf5 46 ISU-E, rEqu c1: 19 ISU-E), ash/olive pollen (rOle e1 29 ISU-E l) and mites (rDerp1 36 ISU-E), in contrast to the recipients where none of these specific IgE were detected. Notably, none of the recipients was atopic either (based on serology). In this case, a kiwi-induced anaphylaxis could not be excluded emphasizing the importance of assessing the allergy profile of the donor at the time of transplantation.

3.4 Diagnosis of IgE sensitization early after transplantation

So far, it remains unclear whether IgE and allergy transfer are affected by the immunosuppressive therapy. Also, the important question whether detection of IgE sensitization is possible early after transplantation is unanswered (17). The overall number of IgE sensitizations of all five atopic recipients remained unchanged within the first 6 months after transplantation (Figure 1E). We therefore decided to study the impact of immunosuppressive therapy on IgE and allergy maintenance. To this purpose, we performed a prospective follow-up analysis on five symptomatic patients with pre-existing allergic rhino-conjunctivitis undergoing living donor kidney transplantation. None of the patients had been treated with anti-histamines at the time of

transplantation. All five patients received a standard induction and maintenance immunosuppressive therapy with basiliximab and methylprednisolone followed by oral tacrolimus, prednisone and mycophenolate mofetil (Figure 2A). SPT and serological analysis were performed before, seven days and 3 months after transplantation, respectively. Surprisingly, the immunosuppressive therapy only moderately affected the skin tests (SPT) results seven days after transplantation (Figure 2B-C) and had no impact on the specific and total IgE levels (Figure 2D-E). Twenty-two of twenty-three and 21/23 of SPT remained positive seven days and three months after transplantation respectively. Finally, the rhino-conjunctivitis score (daily nasal and eye symptoms using a 4-point scale: none, mild, moderate, and severe) before and three months after transplantation did not show a significant improvement (Figure 2F). Overall, these results indicate that IgE sensitization is weakly affected early after transplantation and can be detected based on SPT and IgE serologies despite immunosuppressive therapy.

4. Discussion

4.1 Mechanisms of allergy transfer after SOT

As reviewed in the literature (Table 1), allergy transfer was demonstrated after liver, lung, and pancreas transplantation, but so far not in heart and kidney recipients alone. One could therefore speculate that allergy transfer is a donor organ-specific phenomenon. Interestingly, in the case series reported by Berry et al, allergy transfer occurred in the pancreas-kidney recipient but not in the recipient of an isolated kidney, possibly because of the co-transplantation of a small bowel portion together with the pancreas (6). These data suggest that kidney and heart tissues are less likely to contain sufficient IgG1-memory B-cells (IgG1-MBcs) and/or IgE-producing B-cells (IgE-Bcs) (Figure 3). Thus, the majority of allergen-specific IgE in the blood does not originate from blood-derived B/plasma cells suggesting that local IgE production in tissues is indeed the major source of allergen-specific IgE (18). Furthermore, it is known that persistence of some tissue resident T cells clones can be organ-specific, i.e. influenza specific CD8+T cells are predominantly found in the lungs whereas hepatitis-specific CD8 are predominantly found in the liver (19). The fact that plasmatic IgE can be detected as early as 24 hours after transplantation and that it persists up to several months/years suggests that the primary mechanism lies in the transfer of IgE-producing cells rather than in passive transfer of IgE only, as the half-life of free circulating IgE is known to be only two to four days (20). Interestingly, several groups reported positive SPT without elevation of blood IgE suggesting that IgE alone can be also passively

transferred and secondarily binds to mastocytes, which increases IgE half-life (Table 1, Figure 3) (21). Thus, SPT and IgE serological analysis can be complementary in the diagnosis of allergy transfer.

4.2 Persistence of sensitization and allergy

The persistence of sensitization after allergy transfer in SOT recipients over time is poorly understood. In our series, LiverR1 had detectable IgE for over 393 days (Figure 1C) which turned negative 2 years after transplantation, whereas in LiverSplitR2 peanut-specific IgE were positive for less than 53 days. LiverR1 received an extended liver graft and eventually increased number of passenger leukocytes, but on the other hand LiverSplitR2 has never been exposed to peanut before peanut-specific IgE levels turned negative. Thus, early exposure to allergen after SOT may lead to expansion of IgE-Bcs, or alternatively switch from IgG1-MBcs into IgE producing cells (22) (Figure 3).

Interestingly, in lung transplant recipients, allergy transfer seems to persist longer than in liver recipients (Table1) probably due to the high amount of immune cells in human lung tissue including 100'000 of mast cells per gram of tissue (21). Khalid et al. reported a lung recipient who developed an acute asthma attack without other symptoms of anaphylaxis seven years after transplantation upon exposure to peanuts with negative SPT and negative peanut-specific IgE (Table1, Series 8). This corroborates older data showing that previously non-asthmatic recipients can become asthmatic after lung transplantation from mildly asthmatic donors (23).

Finally, results from hematopoietic stem cell transplantation suggest that matured Th2-like cells or hematopoietic progenitor stem cells are also sufficient to induce and maintain long-term allergy transfer for (more) than 16 years (24). Thus, duration and persistence of the transferred allergy status over time may depend on the organ transplanted and mechanisms of allergy transfer.

4.3 Immunosuppression and allergy

Importantly, our data and that of others (Table 1) indicate that the conventional immunosuppression does not affect IgE-sensitization. This finding is not surprising since donor-specific IgG-producing B cells can mediate acute and/or chronic allograft rejection, two conditions which are associated with limited response to therapy despite several lines of treatments (25, 26). Interestingly, it is also known that IgG producing "passenger lymphocytes" can mediate acute

hemolysis or idiopathic thrombocytopenic purpura within the first two weeks after liver transplantation (27–29).

It has been previously shown that sensitization and allergy symptoms in children after SOT might not be controlled by immunosuppression. On the contrary, the rate of sensitization in patients treated with tacrolimus was even increased (30, 31). Our data from the five living-donor kidney recipients with allergic rhino-conjunctivitis support the observation that diagnosis of donor-derived IgE sensitization based on IgE and SPT is possible early after transplantation despite an immunosuppressive regimen based on basiliximab induction, methylprednisolone/prednisone, tacrolimus and mycophenolate mofetil as maintenance treatment. Further studies assessing the impact on SPT and IgE of other commonly used immunosuppressive drugs, i.e thymoglobulin, azathioprine or rapamycin are warranted.

4.4 Management and patient care

In summary, increased attention has to be given to the risk of allergy transfer after SOT. Unfortunately, the exact frequency and clinical consequences of IgE transfer remains poorly understood as the allergy/atopy status of the donors and recipients are rarely consequently assessed. This is a limitation of the present study, as we focused on donors with fatal anaphylaxis only. In cases of possible or probable fatal anaphylaxis, specific IgE testing in the donor should be performed as one of the first-line investigations to evaluate the possibility of allergy transfer (Figure 4). As donors with a history of severe allergy may die of other reasons than anaphylaxis (Table 1), we would also suggest to carefully explore history of severe allergic reaction to food, hymenoptera venom and drugs with the family of the donor, albeit concise recommendations in this setting are difficult to implement in light of our current knowledge.

Regarding the recipients of organ donors with fatal anaphylaxis, those receiving a liver, lung and pancreas should be closely monitored after transplantation. Furthermore, we encourage to initially check the atopic status of the recipient by the using a qualitative serological screening test (e.g Phadiatop) and measurement of total IgE, as atopic patients may be at a higher risk of allergy transfer. Strict avoidance of eliciting food allergens is strongly advised and emergency medication (including self-injectable epinephrine device) should be prescribed. A detailed allergy work-up as well as follow-up of the sensitization profile is important. In case of donor-derived IgE sensitization transfer, SPT and IgE should be monitored over time. Food challenge should only be considered when SPT and IgE have turned negative (Figure 4) or in cases of low persisting food

specific-IgEs when IgEs to recombinant allergens known to induce severe anaphylaxis are below the threshold level.

In conclusion, we demonstrate that SPT and IgE analysis can be performed as early as 7 days after transplantation. Therefore, postponing investigation the allergological investigation is unnecessary. Prescription of anti-histamines should be omitted in any case seven days prior to SPT as per standard recommendation (17). Finally, good medical practice would include a food challenge to prove tolerance (Figure 4).

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The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Data sharing:
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Figure legends

Figure 1: Allergy transfer analysis in donor and recipients. **A.** Overview of 3 series of donors who died because of fatal anaphylaxis. Green charts show patients with IgE transfer and red charts patients without detectable IgE transfer. Dashed lines highlights recipients with positive oral challenge. § shows atopic recipients. Atopic status was assessed by the presence of specific IgE against, pollen, animal dander or house dusts mites using commercial protein microarray bearing recombinant allergenic molecules (ISAC). **B.** Donors sera analysis with ISAC. Green recombinant IgE highlights those who were transferred into recipients (left Y axis). Yellow bars (right Y axis) represents the tryptase (ng/ml) measured in donors during their hospitalization. **C.** IgE follow-up over time in recipients (liver recipient 1 (LiverR1), liver recipient 2 (LiverSplitR2), lung recipient (LungR3)) of series 1 compared to donor. **D.** Percentage of atopic recipients with or without IgE transfer. **E.** Absolute number of sensitizations before and 6 months after transplantation in all atopic recipients (series1-3).

Figure 2: Allergy persistence in five symptomatic atopic patients. **A.** Immunosuppression protocol of the five recipients over time. **B.** Representative skin prick test results 7 days after transplantation in one of the recipients. **C**. Areas in mm2 of the positive skin prick tests the day before transplantation and 7 and 90 days after transplantation. **D**. Level of total IgE over time (day before transplantation, 7 and 90 days after transplantation) **E.** Level of recombinant IgE over time (day before transplantation, 7 and 90 days after transplantation). **F.** Rhino-conjunctivitis symptoms score before and 90 days after transplantation.

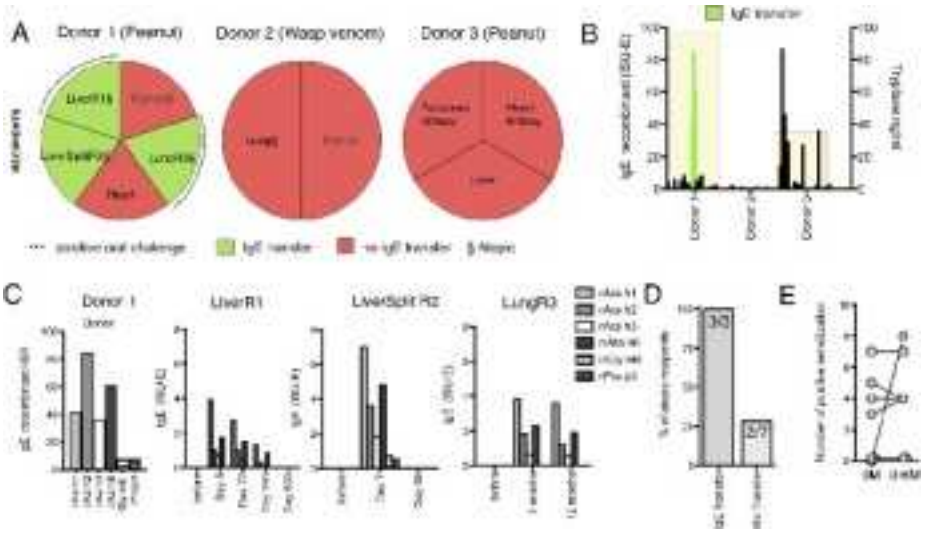
Figure 3: Mechanisms for allergy transfer. Abbreviations: (IgE) Immunoglobulin E. (MC) mastocyte. (IgE-Bsc) IgE producing B cells. (Th) T helper cells, (IgG1-MBcs) IgG1 memory B cells.

Figure 4: Recommendation for patient management in case of solid organ transplantation from donors who died because of fatal anaphylaxis.

Table legend

Table 1: Systematic review of the literature for allergy transfer. Abbreviations: POD (post-operative day), POW (post-operative week).

Table 2: Baseline clinical data of the recipients. Atopic status was assessed by the presence of specific IgE against, pollen, animal dander or house dusts mites using commercial protein microarray bearing recombinant allergenic molecules (ISAC). Abbreviations: (MMF) Mycophenolate mofetil; (MPA) Mycophenolic acid; (TAC) Tacrolimus; (CsA) Cyclosporine. (TX) Transplantation



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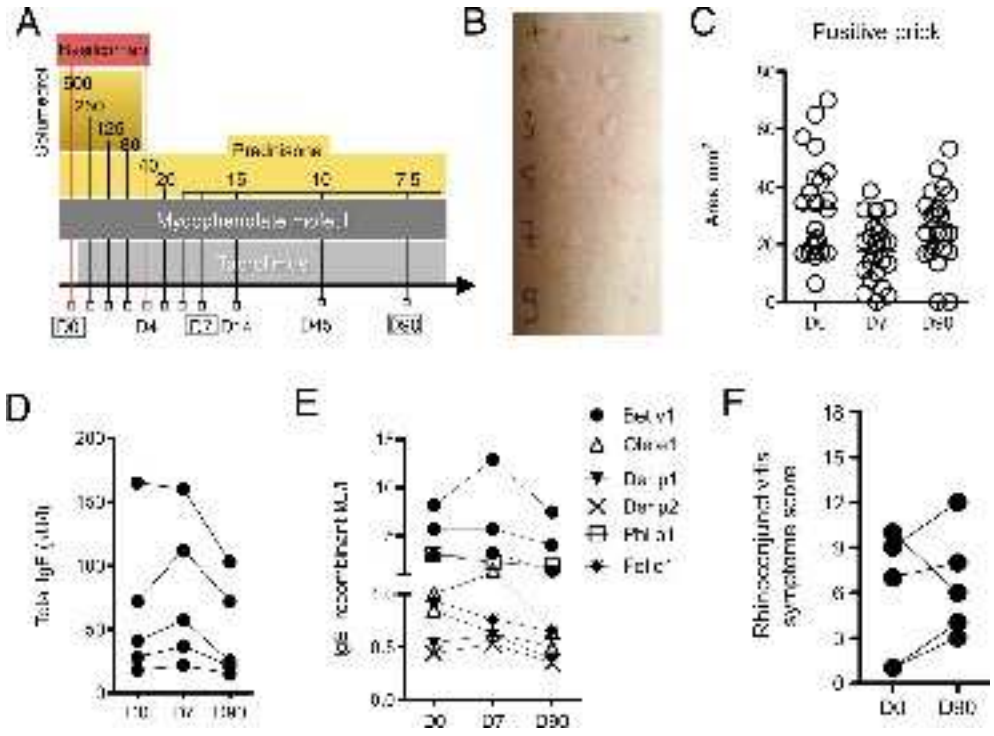

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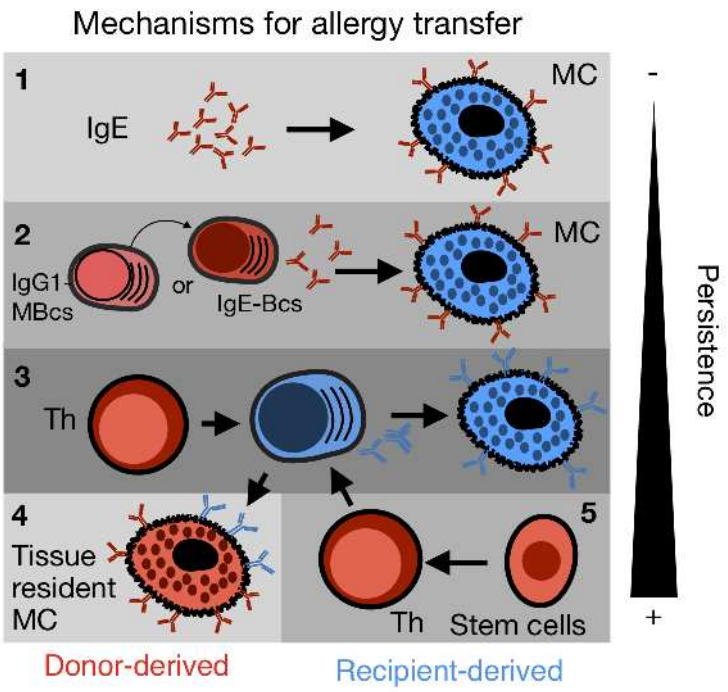

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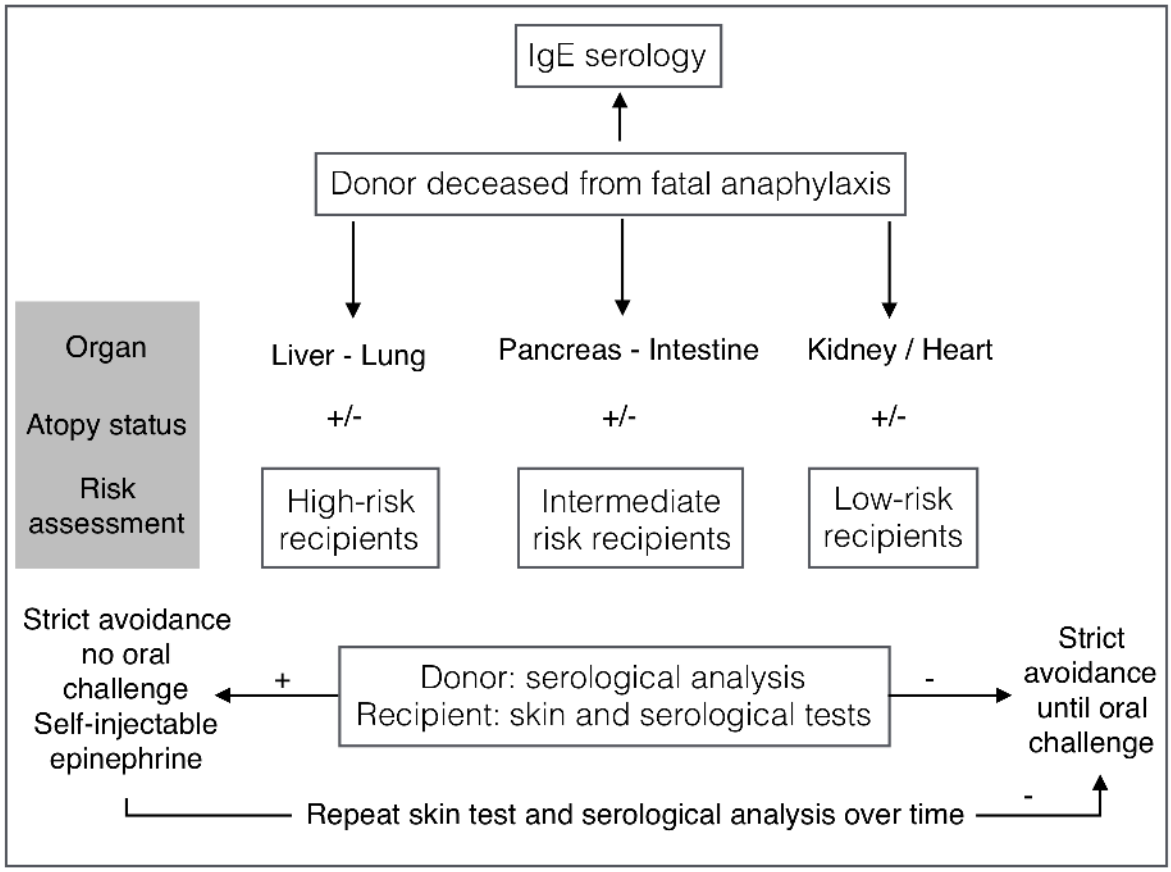

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	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 7	Series 8
Organ(s) with allergy transfer	Liver	Liver	Liver	Liver, Lung	Liver-Kidney	Pancreas-Kidney, Liver (no further information provided)	Lung	Lung
Organ (s) without allergy transfer	Kidney, Kidney-Pancreas	-	Kidney, Kidney, heart	Liver, Kidney, Pancreas	Peancreas-Kidney	Kidney	-	Kidney, Kidney-Pancreas
Cause of donor death	Anaphylaxis	Anaphylaxis	Anaphylaxis	Car accident	Anaphylaxis	Anaphylaxis	Obstructed ventriculoperitoneal shunt	Anaphylaxis
Supposed responsible allergen for death	Peanut	unkown	Peanut	-	Peanut	Peanut	-	Peanut
Donor history of allergy	Atopic dermatitis, asthma	Allergy for nuts, kiwi, seafood, and wheat.	Asthma	Asthma, Peanut allergy	-	Peanut allergy	Peanut allergy (grade 4), allergic rhinitis	Peanut allergy
Anaphylaxis events (Muller classification) in the recipients	POD 25 (grade 2), POW 37 (-)	POD 8 (grade 3)	POD 10 and 28 (grade 1)	Liver POW 8 (grade 4). Lung (-)	POW 12 (grade 3)	-	POW 4 (grade 4)	POD 4 (asthmatic crisis), POW 5 (asthmatic crisis), POW 28 (grade 3),
Time to allergy test	POW 6	POW 3	> POD28	Liver POD 1. Lung POW 4	> POW 12	POW 4	POW 8	> POW 28
Duration of allergy (supposed)	> 48 weeks	> 3 weeks	> 4weeks	Liver < 8weeks Lung > 4 weeks	> 12 weeks	< 24 weeks	< 80 weeks	> 7year
Skin Test	Peanuts, Cashew, Sesame POW 6	Negative	positive POD28 (Peanut)	Liver negative POW 8 Lung positive POW 4 (Peanut)	-	Positive POW 4 (Peanut), Negative POW 24	Positive (POW 8), Negative POW 48	Positive Peanut (>POW 28), Negative 5 years after Tx
IgE serology	Negative	Negative	Negative	Liver postive POD 1 (arah3), negative (POW 20) Lung positive POW 4 (arah1-2-3)	Peanut > POW 12 (rapidly disappeared)	Arah1-2-3 POW 4 Negative POW 24	Negative	Negative (5years after Tx)
Oral challenge	-	Walnuts (grade 3)	-	Liver negative POW 8 Lung positive POW 4	-	Negative POW 24	Negative POW 80	Positive (asthmatic crisis) 7 years after Tx
Immunosuppression	Prednisone, azathioprine, tacrolimus	MMF, prednisone, tacrolimus	Cyclosporine A, prednsione	Liver Cyclosporine , MMF, prednisone Lung Tacrolimus, MMF prednisone	Prednisone, tracrolimus azathioprine	-	Azathioprine, Cyclosporin	Azathioprine, Cyclosporin, prednisione
Atopic status of the recipient	Negative (but no data available)	-	-	Liver - , Lung positive	-	-	Positive	-
Age/Sex of the recipient	60/m	54/m	28/f	Liver 62/f. Lung 54/f	35/m	32/f	47/f	42/f
Reference (PMID)	12546616	19424047	11753913	Liver 21668638, Lung 22172896	9297112	24919754	21766079	18926410
1st Author	Phan et al.	Vagefi et al.	Trotter et al.	Dewachter et al./ Schuller et al.	Legendre et al.	Berry et al.	Bhinder et al.	Khalid et al.

Recipients organ	Donor	Baseline Disease	Atopic status	Age at Tx (years)	Induction Immunosuppression	Maintenance Immunosuppression (6 months)	Maintenance Immunosuppression (12 months)
Heart	1 (peanut)	Dilated cardiomyopathy (antracyclin induced - sarcoma)	Negative	11	ATG, Glucocorticoids, TAC, MMF	TAC, MMF, Glucocorticoids	TAC, MMF, Glucocorticoids
Lung	1 (peanut)	Cystic fibrosis	Positive	25	Basiliximab, CsA, MMF, Glucocorticoids	TAC, MPA, Glucocorticoids	TAC, MPA, Glucocorticoids
Liver left	1 (peanut)	Biliary Atresia	Positive	1	Basiliximab, Glucocorticoids, TAC	Glucocorticoids, TAC	TAC
Liver right	1 (peanut)	PBC (+secondary biliary cirrhosis)	Positive	17	Basiliximab, TAC, MMF	TAC, MMF	TAC, MMF
Kidney left	1 (peanut)	HTA/Renovascular glomerulosclerosis	Negative	76	Thymoglobulin, TAC, MMF, Glucocorticoids	TAC, MMF, Glucocorticoids	TAC, MMF, Glucocorticoids
Lung	2 (wasp)	Cystic fibrosis	Positive	20	Basiliximab, TAC, MMF, Glucocorticoids	TAC, MMF, Glucocorticoids	TAC, MMF, Glucocorticoids
Kidney left	2 (wasp)	Glomerulonephritis/ Vasculitis	Negative	58	Basiliximab, TAC, MMF, Glucocorticoids	Basiliximab, TAC, MMF, Glucocorticoids	Basiliximab, TAC, MMF, Glucocorticoids
Heart and Kidney	3 (peanut)	Ischemic heart disease, HTA/Renovascular glomerulosclerosis	Negative	49	ATG, Glucocorticoids, CsA, MMF	Glucocorticoids, CsA, MMF	Glucocorticoids, CsA, MMF
Liver (left)	3 (peanut)	Sclerosing cholangitis	Negative	5	Basiliximab, TAC, Glucocorticoids	TAC, MMF	TAC, MMF
Kidney Pancreas	3 (peanut)	Diabetic nephropathy (type 1 DM)	Negative	49	Thymoglobulin, TAC, MPA, Glucocorticoids	TAC, MPA	TAC, MPA